



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁴ : A61K 9/20, 31/57		A1	(11) International Publication Number: WO 87/ 05804 (43) International Publication Date: 8 October 1987 (08.10.87)
<p>(21) International Application Number: PCT/US87/00302 (22) International Filing Date: 17 February 1987 (17.02.87)</p> <p>(31) Priority Application Number: 846,620 (32) Priority Date: 1 April 1986 (01.04.86) (33) Priority Country: US</p> <p>(60) Parent Application or Grant (63) Related by Continuation US 846,620 (CIP) Filed on 1 April 1986 (01.04.86)</p> <p>(71) Applicant (<i>for all designated States except US</i>): THE UPJOHN COMPANY [US/US]; 301 Henrietta Street, Kalamazoo, MI 49001 (US).</p>		<p>(72) Inventors; and (75) Inventors/Applicants (<i>for US only</i>) : LERK, Coenraad, F. [NL/NL]; Braamlaan 8, NL-9321 GG Peize (NL). BOLHUIS, Gerard, Klaas [NL/NL]; Noorderstraat 27, NL-9982 HB Uithuizermeeden (NL).</p> <p>(74) Agent: STEIN, Bruce; Patent Law Department, The Upjohn Company, Kalamazoo, MI 49001 (US).</p> <p>(81) Designated States: AT (European patent), AU, BE (European patent), CH (European patent), DE (European patent), DK, FI, FR (European patent), GB (European patent), IT (European patent), JP, KR, LU (European patent), NL (European patent), NO, SE (European patent), US.</p> <p>Published <i>With international search report.</i></p>	
<p>(54) Title: METHYL PREDNISOLONE/SODIUM CARBOXYMETHYL STARCH TABLET COMPOSITION</p> <p>(57) Abstract</p> <p>Micronized, hydrophobic, poorly soluble pharmacologically active agents by use of > 10 % of super-disintegrants are formulated into a powder with good flow properties and a tablet which rapidly disintegrates providing a fast release of the pharmacologically active substance.</p>			

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT Austria	FR France	ML Mali
AU Australia	GA Gabon	MR Mauritania
BB Barbados	GB United Kingdom	MW Malawi
BE Belgium	HU Hungary	NL Netherlands
BG Bulgaria	IT Italy	NO Norway
BJ Benin	JP Japan	RO Romania
BR Brazil	KP Democratic People's Republic of Korea	SD Sudan
CF Central African Republic	KR Republic of Korea	SE Sweden
CG Congo	LI Liechtenstein	SN Senegal
CH Switzerland	LK Sri Lanka	SU Soviet Union
CM Cameroon	LU Luxembourg	TD Chad
DE Germany, Federal Republic of	MC Monaco	TG Togo
DK Denmark	MG Madagascar	US United States of America
EI Finland		

-1-

METHYLPREDNISOLONE/SODIUM CARBOXYMETHYL STARCH TABLET COMPOSITION

BACKGROUND OF THE INVENTION

Glucocorticoid steroids are marketed in many different pharmaceutical dosage forms. In tablet dosage form, the amount of steroid varies greatly. DECADRON Tablets contain 0.25, 0.50, 0.75, 1.5 mg of dexamethasone. MEDROL Tablets contain 2, 4, 8, 16, 24 or 32 mg of methylprednisolone. With prednisone, the tablets contain up to 50 mg of active ingredient. These tablets are produced by use of the usual diluents, binders, disintegration agents, lubricants, coloring agents, etc.

It has now been found useful to administer to patients having certain medical problems such as lymphoma, leukemia, cancer, organ transplant (both pre and postoperatively) or immune complex diseases (rheumatoid arthritis, multiple sclerosis and some kidney diseases), cerebral edema, etc much larger doses of glucocorticoids, in particular methylprednisolone. For example, methylprednisolone has been used in doses of up to 400 mg/m^2 and prednisone has been used in doses of up to $1,000 \text{ mg/m}^2$ in medical oncology. Methylprednisolone has been used in oral doses of 200-2000 mg/day to treat inoperable brain tumors. Since oral administration is preferable, it would be desirable to prepare rapidly disintegrating steroid (methylprednisolone) tablets or capsules containing much larger doses of steroid, in the range of about 50 to about 700 mg for tablets and about 50 to 1000 mg for capsules.

Further, it is desirable to have a tablet or capsule which can either be swallowed or for those individuals who can not swallow a tablet or capsule to have a tablet which will rapidly disintegrate and rapidly dissolve in an aqueous media which can then be drank by the patient. With a capsule, the contents of the capsule can be emptied into the aqueous media. If the tablet is to be produced so that it can be swallowed, it can not be an effervescent tablet. Hence, the larger tablet must be readily dispersible in an aqueous media without being effervescent.

Once a tablet or capsule has disintegrated then dissolution of the active pharmaceutical agent can take place. If one has rapid disintegration then rapid dissolution is possible. If disintegration is slow then rapid dissolution is not possible. Therefore, if one wants a rapid dissolving pharmaceutical agent one should have at

-2-

least a rapid disintegrating tablet.

Most compressed tablets contain a disintegrating agent. A disintegrating agent is a substance, or mixture of substances added to the mixture of ingredients which are used to prepare a tablet, to facilitate the tablet's breakup or disintegration after administration, or disintegration when placed in water to form a solution which can be drank by the patient. The pharmaceutically active ingredient must be released from the tablet matrix as efficiently as possible to allow for its rapid dissolution. If a pharmaceutical agent is released from the tablet slowly it can not have a rapid dissolution rate. Disintegrating agents include (1) starches (corn, potato and rice; corn is the most common), (2) modified starches (sodium carboxymethyl starch also known as sodium starch glycolate), (3) microcrystalline celluloses, (4) water soluble cellulose derivatives (methyl cellulose, sodium carboxymethyl cellulose, hydroxypropyl methyl cellulose and carboxymethylcellulose calcium NF XVI), (5) crosslinked polyvinylpyrrolidones (crospovidone NF XVI), (6) water insoluble cellulose derivatives (croscarmellose sodium, Type A, NF XVI) and (7) others (Veegum HV, agar, bentonite, natural sponge, cation exchange resins, alginic acid, guar gum and citrus pulp).

Some disintegrating agents, super-disintegrants, provide for a more rapid disintegration than others. Super-disintegrants are disintegrants which can be used in a fractional amount of normal disintegrants to obtain the same effect. For example if 2-4 % of a normal disintegrant such as corn starch is used and another disintegrant gives the same effect in a fraction of a per-cent then that disintegrant would be considered a super-disintegrant. Super-disintegrants include modified starches, croscarmellose sodium, carboxymethylcellulose calcium and crospovidone. The pharmaceutical literature indicates that when compared side by side as a tablet disintegrant, with other tablet disintegrating agents, sodium starch glycolate provided the shortest disintegration time; see Pharm. Acta Helv. 44, 418 (1969). Acta Helv. 49, 248 (1974) discloses that sodium starch glycolate is a better disintegrant than others for both water-soluble and water-insoluble pharmaceutical agents. It is known that starch is much more effective as a disintegrant when used extragranularly (in the dry form) or when it is equally distributed outside (in the dry form) and inside (by wet

-3-

granulation) the granules. In contrast to starch, sodium starch glycolate or other super-disintegrants (intragranular, extragranular or equally distributed) have only a small effect on tablet disintegration rate. It is also known that if too much of a water soluble cellulose derivative is used that inhibition of disintegration due to gelatinous entrapment of the tablet particles occurs. This is not true for modified starches (sodium starch glycolate), croscarmellose sodium, type A and crospovidone when used in the common concentrations of about 4%.

Sodium starch glycolate (sodium carboxymethyl starch) is official in the USP XX and NF XV, is marketed under the names EXPLOTAB by Edward Mendell Co. Inc. of New York and PRIMOJEL by Avebe Veendam of Holland. Edward Mendell Co. Inc. in their product literature for EXPLOTAB advertise it as remarkably effective for rapid disintegration and enhanced dissolution when incorporated in tablet formulations prepared by either dry, direct compression or wet granulation techniques. With regard to the amount of sodium starch glycolate to use it states, "Manufacturing experience has suggested that it is most effective in the range of 1-8% with the optimum level in the vicinity of 4%. It is recommended that the proportion to be employed in each individual formulation be determined in the laboratory." Avebe in their product literature for PRIMOJEL state, "PRIMOJEL should be used in concentrations of 2... 8%, calculated on the weight of the tablet. The most usual concentration is about 4%, but in many formulations a concentration of 2% will be sufficient."

Factors other than the presence of disintegrating agents can affect significantly the disintegration time of a compressed tablet. The binder, the hardness of the tablet and the lubricant all influence the disintegration time.

Rapidly dissolving tablets containing 75 to 300 mg of pharmaceutical are known. These tablets usually contain antibiotics which are in their salt form and hence quite water soluble. Tablets containing large amounts of steroid are known. For example, PROVERA Tablets contain 100 and 200 mg of medroxyprogesterone, a hydrophobic substance. Generic medroxyprogesterone tablets containing 400 and 500 mg of the pharmaceutical are known. However, neither the PROVERA Tablets nor the generic medroxyprogesterone tablets are rapidly disintegrating or dissolving.

-4-

Many pharmacologically active powders exhibit a slow dissolution rate because of a low solubility of the solid. For hydrophylic substances the dissolution can be and is generally increased by micronizing the powder (increasing its specific surface area. Most 5 pharmacologically active substances with a low solubility are at the same time hydrophobic. Micronizing such a powder, will give agglomerates which will not deagglomerate in aqueous media, resulting in a decreased dissolution rate, because of a decreased wetted surface. Applying conventional formulations and conventional processing 10 conditions for the formulation of tablets, a slow dissolution rate can be expected, even when the tablets disintegrate rapidly. It is known that if the surface of a hydrophobic pharmaceutical agent is coated with a hydrophylic substance the dissolution time will be decreased. A number of disintegrating agents can serve a dual 15 purpose of being a disintegrating agent and if used to coat the hydrophobic pharmaceutical, a rapid dissolution agent as well. Coating of a hydrophobic pharmaceutical with a disintegrant is only possible when the particle size of the pharmaceutical is much larger than that of the disintegrant. For micronized pharmacologically 20 active ingredients the disintegrant will be coated by the active ingredient.

Contrary to the literature, it has been discovered that large amounts of super-disintegrants (modified starch, croscarmellose sodium, carboxymethylcellulose calcium and crospovidone will provide 25 rapid disintegration.

SUMMARY OF THE INVENTION.

Disclosed is a compressed tablet produced by a wet massing procedure which comprises an effective amount of one or more pharmacologically active substances and greater than about 10 % of a super-disintegrant. 30

Further disclosed is a capsule containing an effective amount of one or more pharmacologically active substances and greater than about 10 % of a super-disintegrant.

DETAILED DESCRIPTION OF THE INVENTION

35 The pharmaceutical composition of the present invention, the compressed tablet, is made following known procedures, in particular wet massing.

The pharmacologically active substances useful with the com-

pressed tablets of the present invention include for example steroids, antibiotics, non-steroidal anti-inflammatory agents, diuretics, anti-epileptics, etc. Examples of steroids include methylprednisolone, medroxyprogesterone, prednisone. Examples of antibiotic 5 include erythromycin, sulfonamides, penicillins, tetracyclines, etc. Examples of non-steroidal anti-inflammatory agents include ibuprofen, flurbiprofen, indomethacin and phenylbutazone. Examples of diuretics include triamterene. Examples of anti-epileptics include phenytoin sodium. Because most of these pharmacologically active substances 10 are slight to extremely strongly hydrophobic it is desirable to coat them with a hydrophilic substance, hydrophilization, in order to have a short disintegration time and a high dissolution rate.

Water soluble cellulose derivatives such as methyl cellulose, sodium carboxymethyl cellulose, etc are hydrophylic substances which 15 are useful in hydrophilization of hydrophobic pharmacologically active substances. Hydrophilization is needed when a coarse hydrophobic agent is formulated into a tablet containing the conventional concentration of a disintegrant (for example 10 - 20 % starch) or super-disintegrant (2 - 8 %). However, the hydrophilization step 20 with methylcellulose has only a limited effect on the dissolution rate of methylprednisolone as compared to the effect of the wet massing procedure when more than 10 % of a super-disintegrant is used. Therefore, it is possible to perform the moistening with water rather than an aqueous mixture of a hydrophilizing agent.

25 The preferred formulation and process for the 100 mg methylprednisolone tablet is found in Example 3. The sequence of the addition of the modified starch, water or the hydrophilizing solution to the pharmacologically active agent(s) is not important for the effect on disintegration of the tablets and the drug dissolution. In 30 a preferred method, the active pharmacological agent(s) is first hydrophilized with an appropriate agent, such as methylcellulose, as is known to those skilled in the art. The super-disintegrating agent is now added. Super-disintegrants include modified starches, croscarmallose sodium, carboxymethylcellulose calcium and crospovidone. The preferred super-disintegrant is the modified starch. It is 35 preferred that the modified starch is sodium carboxymethyl starch. The amount of super-disintegrant is > 10%. It is preferred that the super-disintegrant be present in an amount of from 10 - 60%, more

-6-

preferably 20 - 35%. With methylprednisolone 100 mg tablets it is most preferred the modified starch be present in an amount of about 25 to about 30 %. Sufficient water is added until the mass is in the correct consistency for wet massing. The amount of water needed 5 depends on the amount of microcrystalline cellulose. The mass is then screened or granulated thru an appropriate sized sieve, usually about a 6 mesh sieve. The granules are dried, at about 45 - 55° in a ventilated hot-air oven for about 12 to about 20 hr. Following drying the granules are rescreened using a 500 μm to a 1000 μm sieve, 10 preferably about 750 to about 850 μm . The type of sieve used is determined by the amount of material to be screened, for example with small amounts a 850 μm sieve by hand is operable while with larger amounts an oscillating granulator with a 750 μm sieve is preferred. If desired a diluent, such as, can be added and the material mixed. 15 A lubricant, preferably magnesium stearate, is the last raw material to be added to the mixture before tabletting occurs. While about 0.5 to about 5 % magnesium stearate is operable, 2 or 3 % is preferred as it prevents sticking which can occur if 0.5 % is used. Alternatively, the same result may be obtained by mixing all raw materials 20 (except lubricant) as powders and perform the wetting afterwards.

The tablets are compressed so that the compressed tablet obtained contains the correct quantity of the pharmacologically active substance and meets all required regulatory requirements and disintegrates rapidly. The tablet can be swallowed or put into an 25 aqueous media, allowed to disintegrate and the resulting mixture drank.

While the above formulation and process for the 100 mg methylprednisolone tablet is operable for a larger tablet such as 250 or 500 mg there are some minor changes in the preferred formula and 30 process. The preferred formulation and process for the 250 and 500 mg methylprednisolone tablet is similar to that for the 100 mg with two following two exceptions, (1) no hydrophilizing agent, such as methylcellulose, is used and the intermediate wetting step is omitted. The preferred formulation for a 250 mg methylprednisolone 35 tablet is set forth in EXAMPLE 15.

The capsules of the present invention can be filled with the same granulation as used to make the compressed tablets. It is necessary to have the pharmacologically active substances and > 10 %

-7-

of the super-disintegrant. It is preferable to also have a lubricant such as magnesium stearate. It is well known to those skilled in the art how to prepare pharmaceutical compositions for filling capsules. The capsules will hold up to 1000 mg of pharmacologically active substance. These capsules containing a pharmacologically active substance and > 10 % of super-disintegrant give a rapid disintegration and fast drug release. They can either be swallowed or emptied into aqueous media, allowed to disintegrate and the resulting mixture drank.

10

DEFINITIONS

The definitions and explanations below are for the terms as used throughout the entire patent application including both the specification and the claims.

15

Methylprednisolone refers to $11\beta,17\alpha,21$ -trihydroxy- 6α -methyl-

pregna-1,4-diene-3,20-dione.

Dexamethasone refers to 9α -fluoro- $11\beta,17\alpha,21$ -trihydroxy- 16α -methylpregna-1,4-diene-3,20-dione.

Prednisone refers to $11\beta,17\alpha,21$ -trihydroxypregna-1,4-diene-3,20-dione.

20

Medroxyprogesterone refers to 17α -hydroxy- 6α -methylpregn-4-ene-3,20-dione.

Sodium carboxymethyl starch refers to sodium starch glycolate.

All temperatures are in degrees Centigrade.

25

USP refers to the United States Pharmacopeia.

NF refers to the National Formulary (of the United States).

EXLOTAB refers to sodium starch glycolate marketed by Edward Mendell Co. Inc. of New York, USA.

30

PRIMOJEL refers to sodium starch glycolate marketed by Avebe Veendam of Foxhol, Holland.

Sodium starch glycolate is sodium carboxymethyl starch.

Super-disintegrants are disintegrants which can be used in a fractional amount of normal disintegrants to obtain the same effect.

35

Pharmaceutically acceptable refers to those properties and/or substances which are acceptable to the patient from a pharmacological/toxicological point of view and to the manufacturing pharmaceutical chemist from a physical-chemical point of view regarding composition, formulation, stability, patient acceptance and bioavail-

-8-

ability.

When solvent pairs are used, the ratios of solvents used are volume/volume (v/v).

When the percentage (%) of solid materials is referred to it
5 means on a w/w basis.

EXAMPLES

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, practice the present invention to its fullest extent. The following detailed examples
10 describe how to prepare the various compounds and/or perform the various processes of the invention and are to be construed as merely illustrative, and not limitations of the preceding disclosure in any way whatsoever. Those skilled in the art will promptly recognize appropriate variations from the procedures both as to reactants and
15 as to reaction conditions and techniques.

EXAMPLE 1 Methylprednisolone granulation

Methylprednisolone USP	46.1 %
Microcrystalline cellulose	21.0 %
Sodium carboxymethyl starch	32.9 %

20 The methylprednisolone is hydrophilized with 1.0 % methylcellulose solution (2 gm of methylprednisolone and 1 ml of methylcellulose solution). Three times the amount of methylcellulose solution of water is added to make the mass suitable for granulating.

EXAMPLE 2 Methylprednisolone tabletting composition

Granulate (EXAMPLE 1)	91.2 %
Lactose 100 mesh	8.3 %
Magnesium stearate	0.5 %

30 The granulate of EXAMPLE 1, magnesium stearate, and lactose are mixed for 5 min and then tableted to form compressed tablets containing 100 mg methylprednisolone, meet all regulatory requirements and have the following composition:

Methylprednisolone USP	100.0 mg
Microcrystalline cellulose	45.78 mg
Sodium carboxymethyl starch	71.72 mg
Methylcellulose	0.5 mg
Magnesium stearate	1.095 mg
Lactose 100 mesh	<u>43.65 mg</u>
Tablet weight	262.745 mg

-9-

EXAMPLE 3 10,000 Methylprednisolone 100 mg CT

	Methylprednisolone USP micronized	1,000.	g
	FD and C Blue No 2 Aluminum Lake	1.20	g
5	Methylcellulose USP 15 CPS micronized	5.	g
	Purified water EP-USP	500.	g
	Sodium starch glycolate	714.	g
	Microcrystalline cellulose NF medium po.	456.	g
	Magnesium stearate EP-NF po. food grade	11.	g
10	Purified water EP-USP	q.s.	

CAUTION: 1) Avoid excessive heat and moisture

2) Avoid excessive contact with methylprednisolone

Put the methylprednisolone and the FD and C Blue Nr 2 Aluminum Lake

15 thru a 20 mesh screen, and mix to obtain a sufficiently dispersed color mixture.

Dissolve the methylcellulose in purified water (500 g), add this solution to the above mixture and mix until a proper wetting is obtained.

20 Mix the microcrystalline cellulose and sodium starch glycolate and put thru a 20 mesh screen, add to the steroid mixture and mix 5 min.

25 Add sufficient purified water (about 1,000 ml) to bring to a proper wetness. The wet mass is then processed by hand thru a 6 mesh screen and then air dried at 50° for 16 hr.

The dried granules are then processed thru a Fitzmill with sieve nr 1A.

Magnesium stearate is then processed thru a 20 mesh screen, added to the granulated material and mixed for 3 min.

30 The 2,187 kg mixture is tableted using a 9 mm, rounded, half oval punch with a cross score to give 10,000 tablets with an average weight of 218.7 mg containing 100 mg of methylprednisolone which meets all regulatory requirements.

35 The tablets should be stored in suitable containers, such as double plastic bags with 15 humicaps.

EXAMPLE 4 250 mg Methylprednisolone CT

Following the general procedure of EXAMPLE 3, and making non-critical variations but making tablets averaging 546.75 mg each,

-10-

4,000 compressed tablets are produced each containing 250 mg of methylprednisolone.

EXAMPLES 5-14 Other Compressed Tablets Using > 10% Super-disintegrant

5 Following the general procedure of EXAMPLE 3 and making non-critical variations, and using the pharmacologically active substance of Column A, in an amount of Column B, the compressed tablets of Column C are produced

	<u>Example</u>	<u>Column A</u>	<u>Column B</u>	<u>Column C</u>	
10	5	methylprednisolone	5 kg	10,000 methylprednisolone 500 mg tablets	
	6	medroxyprogesterone	1 kg	10,000 medroxyprogesterone 100 mg tablets	
	7	medroxyprogesterone	1 kg	5,000 medroxyprogesterone 200 mg tablets	
15	8	medroxyprogesterone	2 kg	5,000 medroxyprogesterone 400 mg tablets	
	9	medroxyprogesterone	4 kg	8,000 medroxyprogesterone 500 mg tablets	
	20	10 prednisone	3 kg	30,000 prednisone 100 mg tablets	
25	11	prednisone	6 kg	120,000 prednisone 50 mg tablets	
	12	prednisone	1.4 kg	2,000 prednisone 700 mg tablets	
	13	ibuprofen	60 kg	100,000 ibuprofen 600 mg tablets	
30	14	ibuprofen	60 kg	300,000 ibuprofen 200 mg tablets	

EXAMPLE 15 250 Methylprednisolone CT

	<u>Item</u>	<u>%</u>	<u>Weight in/of final tablet</u>
	Methylprednisolone	57.95	256.1 mg
	FD & C Blue Nr 2 Al Lake	0.055	0.24 mg
	Sodium Starch Glycollate	20.5	90.6 mg
	Microcrystalline Cellulose	19.5	86.2 mg
35	Magnesium stearate	2.0	8.9 mg
	Tablet weight		442 mg

Following the general procedure of EXAMPLE 3 and making non-critical variations including omitting the intermediate wetting step,

-11-

mix all the powders, then granulate with water and compress into tablets.

-12-

CLAIMS

1. A compressed tablet produced by a wet massing procedure which comprises an effective amount of one or more pharmacologically active substances and greater than about 10 % of a super-disintegrant.
5
2. A compressed tablet according to claim 1 where only one pharmacologically active substance is present.
- 10 3. A compressed tablet according to claim 2 where the pharmacologically active substance is selected from the group consisting of steroids, antibiotics, non-steroidal anti-inflammatory agents, diuretics and anti-epileptics.
- 15 4. A compressed tablet according to claim 3 where the pharmacologically active substance is methylprednisolone.
5. A compressed tablet according to claim 3 where the pharmacologically active substance is medroxyprogesterone.
- 20 6. A compressed tablet according to claim 3 where the pharmacologically active substance is prednisone.
7. A compressed tablet according to claim 2 where the pharmacologically active substance is present in an amount from about 50 to about
25 700 mg.
- 30 8. A compressed tablet according to claim 2 where the pharmacologically active substance is present in amounts from about 100 to about 500 mg.
9. A compressed tablet according to claim 1 where the super-disintegrant is selected from the group consisting of modified starches, croscarmallose sodium, carboxymethylcellulose calcium and crospovidone.
35
10. A compressed tablet according to claim 1 where the super disintegrant is a modified starch.

-13-

11. A compressed tablet according to claim 10 where the modified starch is sodium carboxymethyl starch.
12. A compressed tablet according to claim 1 where the modified starch is present in an amount from about 10 to about 60 %.
13. A compressed tablet according to claim 1 where the modified starch is present in an amount from about 20 to about 35%.
- 10 14. A compressed tablet according to claim 1 where the pharmacologically active substance is hydrophobic.
- 15 15. A capsule containing an effective amount of one or more pharmacologically active substances and greater than about 10 % of a super-disintegrant.
16. A capsule according to claim 15 where the pharmacologically active substance is selected from the group consisting of steroids, antibiotics, non-steroidal anti-inflammatory agents, diuretics and anti-epileptics.
- 20 17. A capsule according to claim 15 where the pharmacologically active substance is methylprednisolone.
- 25 18. A capsule according to claim 15 where the pharmacologically active substance is present in an amount from about 50 to about 1000 mg.
- 30 19. A compressed tablet according to claim 15 where the super-disintegrant is selected from the group consisting of modified starches, croscarmallose sodium, carboxymethylcellulose calcium and crospovidone.
- 35 20. A capsule according to claim 19 where the modified starch is sodium carboxymethyl starch.
21. A capsule according to claim 15 where the modified starch is

-14-

present in an amount from about 10 to about 60 %.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 87/00302

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) *

According to International Patent Classification (IPC) or to both National Classification and IPC

⁴IPC : A 61 K 9/20; A 61 K 31/57

II. FIELDS SEARCHED

Classification System	Minimum Documentation Searched ⁷	
		Classification Symbols
IPC	A 61 K	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		

III. DOCUMENTS CONSIDERED TO BE RELEVANT*

Category *	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
X	FR, A, 2121805 (SANDOZ S.A.) 25 August 1972, see page 1, lines 1-4; page 2, line 6 - page 3, line 4; page 3, line 34 - page 4, line 20; page 5, examples 2-4; claims --	1-3,9,14
X	GB, A, 2153677 (FARMITALIA CARLO ERBA SpA) 29 August 1985, see the whole document	1-10,12-19, 20
Y	--	11,20
Y	EP, A, 0052076 (CIBA-GEIGY AG) 19 May 1982, see page 1, lines 22-28; page 5, lines 1-8; page 10, example 4 --	11,20
A	Chemical Abstracts, vol. 98, no. 2, January 1983 (Columbus, Ohio, USA), C.F. Lerk et al., "Interaction of tablet disintegrants and magnesium stearate during mixing. II. Effect on dissolution rate", see page 222, abstract no. 8124n, Pharm. Acta Helv. 1982, 57(10-11), 282-6 --	/. .

* Special categories of cited documents: ¹⁰

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"G" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search

26th May 1987

Date of Mailing of this International Search Report

17 JUN 1987

International Searching Authority

EUROPEAN PATENT OFFICE

Signature of Authorized Officer

M. VAN MOL

International Application No. PCT/US 87/00302

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
A	Chemical Abstracts, vol. 95, no. 24, December 1981 (Columbus, Ohio, USA), H. Robert et al., "Effect of the type and concentration of carboxymethylstarches on the bioavailability of aspirin in tablets", see page 368, abstract no. 209528j, C.-R. - Congr. Eur. Biopharm. Pharmacocinet., 1st 1981, 1, 352-63 -----	

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON

INTERNATIONAL APPLICATION NO. PCT/US 87/00302 (SA 16242)

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 04/06/87

The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
FR-A- 2121805	25/08/72	DE-A, B GB-A-	2200778 1380171
GB-A- 2153677	29/08/85	BE-A- SE-A- FR-A- DE-A- JP-A- NL-A- AU-A- US-A-	901664 8500553 2559065 3503679 60181017 8500323 3848885 4632828
EP-A- 0052076	19/05/82	GB-A, B JP-A- AU-A- CA-A- AU-B-	2086725 57109715 7738281 1178202 552861